DETAILED ACTION

Status of the Claims

1. Claims 34-51 and 54 remain pending. Claims 52-53 are cancelled. Claims 55-61 are newly added. Claims 34, 35 and 38 are amended.

Response to Previous Rejections

2. In light of amendment of the claims, the previous rejection under 35 USC § 112, second paragraph is withdrawn.

3. Applicant argues that the previous rejection of the claims under 35 USC § 103(a) does not apply to the presently amended claims and should therefore be withdrawn. Applicants' arguments have been carefully considered but have not been found to be persuasive.

4. It appears that the Examiner and Applicants are in agreement that the primary reference, Avrahami (US Patent No. 6,148,232) discloses a method encompassed by independent claim 34, section (i), from which all other claims depend:

> [G]enerating a plurality of micro-channels[1] in a region of intact skin[2] of a subject by an apparatus that comprises: (a) an electrode cartridge comprising a plurality of electrodes; and (b) a main unit comprising a control unit, which is adapted to apply electrical energy to the electrodes when the electrodes are in vicinity of the stratum corneum of the skin, enabling ablation of the stratum corneum in the region beneath the electrodes, thereby generating the plurality of micro-channels[3]

Whether Avrahami utilizes a commercially available skin patch is irrelevant to the claim as section (ii) of the method claim requires affixing a patch (*emphasis added*) to the skin where the micro-channels created in section (i) are found. *See* Applicants' response at page 7, first full

---

[1] Avrahami discloses formation of micro-channels (plural) at least at Column 3, lines 38-44.
[2] *See* Avrahami at Column 3, lines 3-6 where the micro-channels extend through all the stratum corneum.
[3] *See* Avrahami at Column 2, lines 27-29, 59-67 which also discloses use of a skin patch to the region of skin where micro-channels have been formed.

paragraph. The secondary references, under section 103, relate to the patch that is affixed in this region. It is important to also recognize that the claims are drawn to a method, not to a product.

5. With regard to the secondary reference Venkatraman *et al.* (US Patent No. 6,275,728), Applicants argue that the patch of Venkatraman *et al.* includes an electrode layer and a reservoir layer for the agent to be iontophoretically delivered. *See* Applicants' response at page 8, lines 1-5. Applicants further assert that in the instant invention, transdermal delivery of the peptide, polypeptide or protein is by diffusion only. *See* Applicants' response at page 8, lines 14-16. Applicants point to paragraphs [0017] and [0059] of their published application (US Patent Application Publication No. US 2007/0287949) for support of this argument of passage by diffusion only. The cited paragraphs do not provide support for the contention that the invention at the time of filing encompassed a method whereby passage of peptides, polypeptides or proteins occur by diffusion only. In fact, [0059] states that micro-channels provide pores through "all or a significant portion of the stratum corneum and may reach into the epidermis or dermis, through which molecules can diffuse." *Emphasis added.* This clearly does not provide support for the argument for passage of the molecules through the stratum corneum by diffusion only. Further, it is worth noting that the primary reference discloses "micro-channels allow the diffusion therethrough of large molecules at a greater rate than the same molecules would diffuse through pores generated by electroporation." *See* Avrahami, Column 3, lines 8-10. Thus, diffusion of large molecules (i.e. peptides, polypeptides and proteins) through micro-channels is recognized by the primary reference.

6. With regard to Venkatraman *et al.*, passage of the therapeutic agent may also occur via diffusion, the claimed method is open language (comprises) which would include transport by

mechanisms in addition to diffusion and the claim is not so narrow to be limited to *diffusion only*, as Applicants have argued. Since the claim has not been amended for diffusion only, there is no issue of new matter; rather, it has been argued to be diffusion only.

7. With regard to Song *et al.* (US Patent No. 5,418,222), Applicants argue that Song *et al.* is limited to use of their collagen film only for wound, burn or trauma sites of the skin. First, it should be recognized that the primary reference focuses on placement of the patch over intact skin where micro-channels have been formed. *See* Avrahami, Column 3, lines 3-6: "The term 'micro-channel' as used in the context of the present patent application and in the claims refers to a pathway generally extending from the surface of the skin through all or a significant part of the stratum corneum" which is strikingly similar to Applicants' [0059] recited above. Thus, the primary reference already contemplates micro-channel formation over intact skin. Second, Song *et al.* is not limited to only wound, burn or trauma sites. Other aspects, which precede the paragraphs discussing wound, burn or trauma sites are broader.

8. With regard to Haak *et al.* Applicants argue that the reference focuses on iontophoretic drug delivery devices. As discussed above, and in the context of section (ii) of claim 34, Haak *et al.* still reads on the claim.

9. With regard to Farinas, Applicants argue that the preferred embodiment focuses on hydrophobic polymers, while neglecting the fact that Farinas provides a number of polymeric matrices, including those claimed by Applicants (which are hydrophilic) and cited in the previous Office Action. Further, the claim language remains open "wherein the drug reservoir layer comprises a hydrophilic polymeric matrix" which would include polymeric matrices beyond just those that are hydrophilic. Regarding the statement that there are no patches in

Farinas, Applicants attention is directed to Column 3, lines 5-10, which describe a transdermal system comprising a laminated composite of a backing layer and a contact adhesive layer which contacts the skin.

10. With regard to Phipps, Applicants argue that Phipps includes electrotransport of drug delivery. As discussed above, the method claims remain open and still read on the prior art.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 34-51 and 54 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Avrahami (US Patent No. 6,148,232, issued Nov. 14, 2000) in view of Venkatraman *et al.* (US Patent No. 6,275,728, issued August 14, 2001) in view of Phipps *et al.* (US Patent No. 5,983,130, issued Nov. 9, 1999) in view of Song *et al.* (US Patent No. 5,418,222, issued May 23, 1995) in view of Haak *et al.* (US Patent No. 5,158,537, issued Oct. 27, 1992) in view of Farinas *et al.* (US Patent No. 5,906,830, issued May 25, 1999).

13. Avrahami (the '232 patent) discloses a method for using a device for enhancing transdermal movement of substances, wherein said device comprise a skin patch, electrodes, a control unit coupled to the patch which passes current through the electrodes through the stratum corneum epidermidis in order to generate at least one micro-channel in the stratum corneum to enable or augment transdermal movement of the substance (Column 2, lines 59-67). The device can create the micro-channels, then be removed from the skin, and a commercially-available skin

patch can be placed over the skin with the micro-channels (Column 6, lines 29-33). Thus, Avrahami provides the teaching that a device for creating micro-channels, for the purpose of enhancing transdermal delivery of therapeutics by diffusion through microchannels, can be combined with transdermal skin patches.

14. Avrahami does not disclose the particular skin patches used in combination with this methodology as these items are taught in other aspects of the prior art. Numerous patents, detailed below, describe electroporation devices as well as transdermal delivery devices, including sustained release transdermal delivery devices.

15. Transdermal skin patches are well known in the art, as evidenced by numerous patents. For example, Song *et al.* (the '222 patent) discloses single and multiple layer collagen films for sustained release delivery of pharmaceuticals (Abstract). Song *et al.* also disclose that electroporation, by itself, does not deliver drug, it prepares the tissue for delivery of drug by other means, including iontophoresis (Column 3, lines 37-42). Song *et al.* further disclose delivery of insulin and HGH for transdermal electrotransport delivery of peptides and polypeptides (Column 13, lines 39-50).

16. Venkatraman *et al.* (the '728 patent) disclose a hydratable drug reservoir film for electrotransport drug delivery devices (Abstract). These devices can deliver charged or uncharged substances into the body (Column 2, lines 10-16). The electrotransport delivery device (i.e. patch) includes a drug reservoir layer (Column 2, lines 32-33). The system is useful for controlled delivery of peptides, polypeptides and proteins (Column 7, lines 1-3). The drug reservoir can comprise hydrophilic polymers like polypropylene oxide and polyethylene oxide (Column 8, lines 21-22).

17. Phipps *et al.* (the '130 patent) discloses an electrotransport agent delivery device for delivering a therapeutic agent through a body surface (Abstract). The electrotransport delivery devices can be used to deliver uncharged drugs or agents into the body transdermally (Column 2, lines 14-21). The devices include a reservoir of the agent which is to be delivered into the body by electrotransport (Column 2, lines 22-26). The application of electric current through the skin is known as electroporation which creates pores in lipid membranes due to reversible electrical breakdown (Column 3, lines 25-42). This transdermal electrotransport delivery device is useful to transport agents such as peptides, polypeptides, insulin and HGH (Column 13, lines 39-50).

18. Farinas *et al.* (the '830 patent) discloses transdermal drug delivery systems comprising drug reservoirs wherein polymeric materials which are suitable for such devices include gelatin and carrageenan (Column 6, lines 61-67 and Column 7, lines 1-19).

19. It would have been obvious and well within the level of skill of one of ordinary skill in the art to take the motivational teaching of the '232 patent to perform electroporation of the skin followed by placement of a sustained delivery transdermal patch on the electroporated area of the skin in order to deliver a therapeutic or immunogenic agent (peptide, polypeptide or protein) using a patch loaded with such agents, as these type of patches, transdermal delivery methods and combinations thereof for sustained transdermal delivery are well known in the prior art (the '728 patent, the '222 patent, the '130 patent, the '537 patent and the '830 patent).

Claim 34

20. The '232 patent discloses a method for transdermal delivery of therapeutic agents by creating micro-channels in the skin (Column 2, lines 59-67) followed by placement of a transdermal patch over the micro-channels on the skin (Column 6, lines 29-33). The "micro-

channels allow the diffusion therethrough of large molecules at a greater rate than the same molecules would diffuse through pores generated by electroporation" (Column 3, lines 8-10). The diffusion of large molecules is through intact skin "The term micro-channel as used in the context of the present patent application and in the claims refers to a pathway generally extending from the surface of the skin through all or a significant part of the stratum corneum." (Column 3, lines 3-6). The '728 patent discloses a patch with a drug reservoir (Column 2, lines 32-33) comprising peptides, polypeptides or proteins (Column 7, lines 1-3). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '728 patent to arrive at the invention of claim 34.

Claims 35, 38, 39 and 40

21. The '728 patent further discloses that the drug reservoir comprises hydrophilic polymers (Column 4, lines 21-23) like polypropylene oxide and polyethylene oxide (Column 8, lines 21-22). The drug reservoir may be dry (Column 1, lines 12-14). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '728 patent to arrive at the invention of claims 35 (hydrophilic polymers), 38 (polypropylene oxide and polyethylene oxide), 39 (polyethylene oxide) and 40 (dry or semi-dry form drug reservoir). The '222 patent also discloses a dry collagen solution (Column 4, lines 11-12). The '537 patent also discloses polyethylene oxides, hydroxyethyl cellulose and chitosan (Column 15, lines 1-20; claim 36) and polyurethane (Column 15, lines 30; claims 38 and 39).

Claims 36-37

22. The '222 patent discloses collagen film patches with drug reservoir layers for improved sustained release delivery of pharmaceuticals through the skin (Column 1, lines 13-15, Column

2, lines 11-15 and lines 32-35). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '222 patent to arrive at the invention of claims 36 and 37 (biopolymer is collagen).

Claims 41-43

23. The '222 patent discloses that the therapeutic within the drug reservoir can be a growth factor, particularly PDGF, EGF, FGF or TNF (Column 2, lines 40-44), while the '728 patent references (and incorporates by reference) US Patent No. 5,158,537 which provides examples of peptides and proteins which may be delivered using the transdermal delivery device disclosed therein. The '537 patent discloses that the therapeutic within the drug reservoir can be insulin or growth hormone (Column 13, lines 55 and 58). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '222, '728 and '537 patents to arrive at the invention of claims 41 (growth factors), 42 (insulin, PDGF, EGF, FGF, TNF, HGH) and 43 (HGH or insulin).

Claims 44 and 45

24. As the '222 patent teaches, collagen films are useful for sustained transdermal delivery of protein therapeutics, which have been exemplified with polypeptide growth factors (Column 1, lines 13-15, Column 2, lines 40-43). For this reason, it would naturally flow to combine a sustained delivery collagen matrix, with therapeutic agents such as insulin or HGH. It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '222, '728 and '537 patents to arrive at the invention of claims 44 (collagen and HGH) and 45 (collagen and insulin).

Claims 46-51 and 54

25. The '728 patent discloses that the drug reservoir of a transdermal drug delivery device can comprise polyethylene oxide (Column 8, lines 21-22). The '830 patent discloses suitable polymeric materials for a transdermal drug delivery system which includes carrageenan (Column 6, lines 61-67 and Column 7, lines 1-19). The '222 patent discloses collagen films coupled with an adhesive (Column 1, line 41) as well as the use of buffering agents (Column 4, lines 66-68). The '232 patent discloses an apparatus comprising an electrode cartridge with a plurality of electrodes, a main unit comprising a control unit, adapted to apply electrical energy to the electrodes thus enabling ablation of the stratum corneum to generate at least one micro-channel (Column 2, lines 59-67). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '728 patent to arrive at the invention of claims 46 (polyethylene oxide and insulin) and 47 (polyethylene oxide and HGH). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '830 patent to arrive at the invention of claims 48 (carrageenan and HGH) and 49 (carrageenan and insulin). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '222 patent to arrive at the invention of claim 50 (a patch with at least an adhesive) and claim 51 (using of a buffering agent). The '232 patent discloses an apparatus comprising an electrode cartridge with a plurality of electrodes, a main unit comprising a control unit, adapted to apply electrical energy to the electrodes thus enabling ablation of the stratum corneum to generate at least one micro-channel (Column 2, lines 59-67; now incorporated into claim 34). Applicant has further admitted the use of radio frequency is known in the prior art (see page 11, lines 20-24 of the instant specification where the commercially available products are referenced; claim 54).

Newly Rejected Claims 55-61

26. Claim 55 recites that the buffering agent is selected from the group consisting of acetate buffer, phosphate buffer and citrate buffer. Song *et al.* disclose the same three buffers in their composition (Column 4, lines 67-8 to Column 5, lines 1-2). Claim 56 recites a suitable pH range of from about 3 to about 8. Song *et al.* also disclose that a suitable pH is from about 3 to about 8 (Column 5, line 7). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '222 patent to arrive at the invention of claims 55 and 56.

27. Claim 57 recites that the hydrophilic polymeric matrix is a cellulose derivative. Farinas *et al.* disclose methylcellulose and carboxymethylcellulose (Column 7, line 13). Claim 58 recites that the patch comprises ethylene-vinyl acetate copolymer. Farinas *et al.* disclose use of the same (Column 6, lines 66-67). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '830 patent to arrive at the invention of claims 57 and 58.

28. With regard to claim 59, all components of claim 34, from which claim 59 depends, have been disclosed in the prior art. Since the prior art discloses the same structural components, they must necessarily possess the claimed inherent property. For this reason, claim 59 is obvious.

29. With regard to claims 60 and 61, the claims specify that the pharmaceutical composition comprises a sugar, particularly mannitol, lactose, sucrose, trehalose or glucose. Song et al. disclose the use of stabilizing agents including sugars, preferably mannitol, lactose and glucose (Column 4, lines 48-50). It would have been obvious to one of ordinary skill in the art to combine the teachings of the '232 patent and the '830 patent to arrive at the invention of claims 60 and 61.

Conclusion

30. No claim is allowed.

31. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DEVESH SRIVASTAVA whose telephone number is (571) 270-3288. The examiner can normally be reached on Monday - Friday 8:00 - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DEVESH SRIVASTAVA/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
Art Unit 1615